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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,122	OGLE ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-10,13-17,51 and 52* is/are pending in the application.

4a) Of the above claim(s) *9,10,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,8,13,14 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed December 14, 2010. Claims 1-10, 13-17, 51 and 52 were previously pending, with claims 9, 10, 16 and 17 withdrawn from consideration. Applicants amended claims 1, 3 and 4 and cancelled claims 2 and 6. Claims 1, 3-5, 7, 8, 13-15, 51 and 52 will be examined.

2. Applicants' amendments did not overcome the previously presented rejections for reasons given in the 'Response to Arguments" below. This office action contains new grounds for rejection necessitated by amendment.

Response to Arguments

3. Applicant's arguments filed December 14, 2010 have been fully considered but they are not persuasive.

Regarding the rejection of claims 1-8, 13-15, 51 and 52 under 35 U.S.C 103(a) over Arstila et al., Wagner et al., Lebed et al., Kamb et al., Cho et al. and Piechocki et al., Applicants argue the following:

i) Neither Arstila et al. nor Wagner et al. quantify diversity. Arstila et al. do not enumerate TCR V beta chains, and Wagner et al. determines frequencies of V-J sequences, but does not enumerate TCR V beta diversity.

ii) The cited prior art does not teach determining the frequency of hybridization, only the detection of intensities.

Regarding i), Applicants did not limit the claims to any particular regions containing the TCR Vbeta. Further, both Arstila et al. and Wagner specifically determine the number and frequency of the Vbeta regions: see Arstila et al., page 958, second paragraph and Table 1, for example; and Wagner et al., Abstract; page 14447, third paragraph; page 14448, fourth paragraph;

Fig. 1-4. Therefore, these references specifically teach detection of lymphocyte diversity. Regarding ii), as indicated below, both Arstila et al. and Wagner et al. teach frequencies of different Vbeta regions. Therefore, whether determined by nucleic acid amplification and fragment sorting by length, or by nucleic acid hybridization to probes, one of skill in the art would have no problem with determining the frequency of each sequence in the population.

The rejection is maintained.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3-5, 7, 8, 13-15, 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A) The claims are rejected over the recitation of "the frequency of hybridization in each of said discrete regions". There is no support in the specification or in the originally filed claims for this limitation. Applicants did not describe determination of the hybridization frequencies at each separate array locations, but the total number of signals summed up over all locations. Therefore claim 1 as amended introduces new matter.

B) Claims 3 and 4 lack written description. Applicants amended claim 1 to read "wherein said solid substrate comprises a plurality of discrete regions, wherein each of said discrete regions

comprises a different random nucleic acid molecule". The dependent claims 3 and 4 recite a bead as solid support. Applicants did not describe how a bead can be partitioned into different regions containing distinct nucleic acid probes.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 3-5, 7, 8, 13-15, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arstila et al. (Science, vol. 286, pp. 958-961, 1999; cited in the IDS and in the previous office action), Wagner et al. (PNAS USA, vol. 95, pp. 14447-14452, 1998; cited in the IDS and in the previous office action), Lebed et al. (J. Biomol. Struct. Dynam., vol. 18, pp. 813-823, 2001; cited in the previous office action), Kamb et al. (U.S. Patent No. 6,060,240 A; issued May 2000; cited in the previous office action), Cho et al. (Appl. Env. Microbiol., vol. 68, pp. 1425-1430, March 2002; cited in the previous office action) and Piechocki et al. (J. Immunol. Meth., vol. 259, pp. 33-42, January 2002; cited in the previous office action).

A) Regarding claims 1 and 13-15, Arstila et al. teach determining lymphocyte diversity in a subject by obtaining cDNA from T-cells of a subject and amplifying the cDNA encoding CDR3 region of the TCR β receptor with Vβ-, Jβ- and Cβ-specific primers, followed by gel separation of amplified products and sequencing (page 958; page 959, first and third and fourth paragraphs; Fig. 1 and 2). They teach obtaining frequencies of different chain sequences (page 958, second paragraph).

Regarding claims 1 and 13-15, Wagner et al. teach determining lymphocyte diversity in rheumatoid arthritis patients by amplification of cDNA encoding CDR3 region of the TCR β receptor from CD4 T-cells with Vβ- and jβ-specific primers, followed by cloning and sequencing or hybridization to TCR N-D-N probes (page 14448, paragraphs 2-3 and 8; page 14449, first and second paragraph). They teach obtaining frequencies of different chain sequences (Abstract; Fig. 1-4).

B) Neither Arstila et al. nor Wagner et al. teach hybridization of nucleic acids derived from lymphocytes to random nucleic acid molecules in order to determine lymphocyte diversity.

C) Regarding claims 1 and 13-15, Lebed et al. teach application of random oligonucleotide arrays to the determination of the CDR3 regions diversity in lymphocytes (page 813, last paragraph; page 814; page 815, paragraphs 1-3). Lebed et al. teach random hexamers immobilized in different parts of the chip (page 814, second paragraph).

Regarding claim 3, Lebed et al. teach a chip (page 814, second paragraph).

Regarding claim 7, Lebed et al. teach nucleic acids labeled with fluorophores (page 815, first paragraph).

Regarding claim 52, Lebed et al. teach labeled DNA molecules (page 815, first paragraph).

D) Regarding claim 1, Kamb et al. teach a method comprising:

a) providing:

i) labeled nucleic acid molecules from a sample (col. 6, lines 7-11 and 28-38; col. 17, lines 29-42),

ii) a population of nucleic acid molecules, wherein said population of nucleic acid molecules comprises random nucleic acid molecules (Fig. 6; col. 14, lines 23-64; col. 24, lines 58-62);

b) hybridizing said labeled nucleic acid molecules or fragments of said labeled nucleic acid molecules with said population nucleic acid molecules (col. 6, lines 5-11 and 29-35);

c) assessing hybridization of said labeled RNA nucleic acid molecules with said population of nucleic acid molecules to determine the frequency of hybridization (col. 6, lines 35-38), and

d) quantifying the amount of hybridized nucleic acid (col. 6, lines 35-38; col. 24, lines 58-67; col. 25, lines 1-28).

Regarding claims 3 and 4, Kamb et al. teach beads (col. 5, lines 63-67; col. 6, lines 1-7; col. 9, lines 31-48; col. 10, lines 36-54).

Regarding claim 5, Kamb et al. teach flow cytometry (col. 6, lines 10, 11; col. 21, lines 25-39).

Regarding claim 7, Kamb et al. teach fluorophore labels (col. 6, lines 8, 9, 31, 32; col. 17, lines 29-42; col. 21, lines 25-39).

Regarding claim 8, Kamb et al. teach phycoerythrin (col. 21, line 64).

Regarding claims 51 and 52, Kamb et al. teach labeling mRNA or cDNA (col. 6, lines 30-32).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used solid support-bound random oligonucleotdes of Lebed et al. or Kamb et al. in the methods of detecting T-cell diversity of Arstila et al. and Wagner et al. The motivation to do so is provided by Kamb et al. (col. 5, lines 43-47):

"The methods of the invention also provide other advantages, such as increasing the throughput of probes, boosting the generation of valuable data, and significantly lowering the time and cost of analysis."

Further, considering the fact that the estimated TCR diversity of Arstila et al. was of the order of 10^6 (Table 1), using the random 15mer probes of Kamb et al. would provide 4^{15}, or 1.1 x 10^9 different capture probes (col. 24, lines 62-64), allowing in principle capture of every single TCR variant present in a given cell type. Further, considering that FACS machines sort beads with a rate of about 100 million per hour (col. 21, lines 32-33), analysis of a multitude of different samples can be performed rapidly.

The motivation to do so is also provided by Wagner et al. (page 14452, last paragraph):

"Regardless of the precise mechanism for the loss of T cell diversity, these aberrations have important implications for the disease process and the way it is treated and studied. The fact that large proportions of the TCR repertoire are altered cannot remain without consequences for immunoresponsiveness. It is possible that the repertoire contraction will generate holes in the repertoire and therefore will lead to defective immune responses to selected antigens. The design of therapeutic approaches should consider that the RA repertoire already has lost diversity. So far, it has been assumed that it would be beneficial to deplete T cells. If these patients have difficulties repopulating the T cell compartment and have to generate new T cells through self-replication, T cell-directed therapies will compromise further their ability to maintain diversity. It is, therefore, not surprising that treatment trials using T cell depletion were not successful and had substantial side effects (31, 41). Very different therapeutic approaches will have to be taken to correct repertoire aberrations in an attempt to control the disease process and its complications."

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention that as precise as possible determination of lymphocyte diversity enabled effective diagnosis and treatment of infections and immune diseases.

E) None of the above references teaches quantitation of the amount of hybridized nucleic acids based on standard curves.

However, quantitation of either microarray data or flow cytometry date was known in the art of the invention, as evidenced by Cho et al. and Piechocki et al.

Cho et al. teach determining a number of expressed genes from array hybridization using standard curves obtained by hybridizing samples with known numbers of gene copies to an array of oligonucleotides, and creating a standard curve based on the measurements (page 1425, second paragraph; Fig. 1, 2; page 1426, last paragraph; page 1427; Fig. 3).

Piechocki et al. teach quantitation of anti-ErbB2 antibodies by flow cytometry based on standard curve (Abstract; page 35, first paragraph; page 38, last paragraph; page 39, first paragraph; Fig. 5).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to perform quantitative measurements of the T-cell diversity in the method of Arstila et al., Wagner et al., Lebed et al. and Kamb et al., since the diversity was measured as the total number of different sequences present in samples.

Further, since either array hybridization data or bead hybridization data are presented for each spot or bead, the frequency of each type of the sequence present can be assessed in a manner analogous to the frequency determination as taught by Arstila et al. and Wagner et al.

9. No claims are allowed.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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February 11, 2011